PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 110087101	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/SE2003/001598	International filing date *(day/month/year)* 15.10.2003	Priority date *(day/month/year)* 16.10.2002
International Patent Classification (IPC) or national classification and IPC A61K 45/06, A61K 9/00, A61P 1/04 // A61K 31/4439, A61K 31/4164, A61K 31/341, A61K 31/426		
Applicant Orexo AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.05.2004	20.01.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001598

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority is considered valid. Therefore, the document cited in Box No. VI is of no particular relevance.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International Application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-39 partly, 40-48

because:

☒ the said international application, or the said claims Nos. 40-48 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-39 partly are so unclear that no meaningful opinion could be formed *(specify)*:

Present claims 1-39 relate to dosage forms, and to methods for the production of these dosage forms, defined by references to desirable properties, namely "acid-susceptible proton pump inhibitor", "H2 receptor antagonist", "pharmacologically effective amounts", "delayed release and/or extended release"

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. III

and "rapidly released". The claims cover all dosage forms having these properties and all methods for the production of dosage forms having these properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such dosage forms and methods.

Independent of the above reasoning, claims 1-39 also lack clarity (Article 6 PCT). An attempt is made to define the products by reference to a result to be achieved. This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Specifically, the terms "acid susceptible proton pump inhibitor" and "H2 receptor antagonist" apparently relate to a very large amount of different compounds, which do not necessarily have to be defined as acid susceptible proton pump inhibitors or H2 receptor antagonists, thus rendering it impossible to perform a complete search.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the present claim 2 in combination with the present claim 4, as well as the present claim 37 in combination with the present claim 38.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-39	YES
	Claims	-	NO
Inventive step (IS)	Claims	-	YES
	Claims	1-39	NO
Industrial applicability (IA)	Claims	1-39	YES
	Claims	-	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: Canadian pharmaceutical journal, Volume 135, no. 7, 2002, Doret Cheng: 'Combined use of proton pump inhibitors and histamine-H2 receptor antagonists for GERD: What is the rationale?', pages 27- 45.
D2: US6183776
D3: Gastroenteroloy, Volume 115, 1998, Paolo L. Peghini et al: 'Ranitidine Controls Nocturnal Gastric Acid Breakthrough on Omeprazole: A Controlled Study in Normal Subjects', pages 1335-1339.
D4: WO9311750
D5: Br. J. Clin. Pharmac., Volume 31, 1991, Tommy Andersson et al: 'Influence of acid secretory status on absorption of omeprazole from enteric coated granules', pages 275-278.
D6: WO9725065
D7: Baillière's Best Practice & Research Clinical Gastroenterology, Volume 15, no. 3. 2001, Philip O. Katz MD et al: 'Histamine receptor antagonists, proton pump inhibitors and their combination in the treatment of gastro-oesophageal reflux disease', pages 371-384.
D8: US5204118
D9: WO9904773

The invention according to present claims 1-29 relates to an oral pharmaceutical dosage form comprising an acid-susceptible proton pump inhibitor (PPI) and an H2 receptor antagonist (H2RA), and at least one excipient which results in delayed and/or extended release of the PPI. The H2RA is included in such a way that it is rapidly released from the dosage form. The term "dosage form" is defined as including both separate

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. V

doses administered concurrently and doses combined in the same preparation. The invention according to claims 30-38 furthermore relates to a method for the manufacture of the dosage form, whereas the invention according to claim 39 relates to use of the dosage form for the manufacture of a medicament against conditions associated with the secretion of gastric acid.

D1 describes a study of the combined use of PPI:s and H2RA:s for the treatment of GERD. It is concluded that some patients may benefit from the addition of an H2RA to the bedtime dose of the PPI in twice daily PPI therapy. The combination in D1 is considered to fulfil the criteria of a "dosage form" as defined in the application.

D1 can be chosen to represent the closest prior art. The invention according to claim 1 apparently differs from the prior art according to D1 in two aspects: firstly, in the inclusion of an excipient which results in delayed and/or extended release of the PPI, and secondly, in the rapid release of the H2RA. The problem solved by these aspects of the invention is the provision of a both rapid and long-acting acid suppression.

Regarding the first aspect mentioned above are both delayed and extended release formulations of PPI:s known to the person skilled in the art. This can be exemplified by D2, providing a delayed release formulation. D2 (abstract; col. 3, lin. 64 - col. 4, lin. 6; col. 8, lin. 24-25; col. 8, lin. 54-63) thus discloses an oral pharmaceutical dosage form for use in the treatment of disorders associated with dyspepsia, which dosage form comprises an acid-susceptible PPI or an H2RA in admixture with excipients (such as binders) in a tablet core protected by an enteric coating layer and an optional separating layer, and a surrounding layer comprising one or more antacid agent(s) or an alginate in admixture with excipients. Said enteric coating layer provides the delayed release. It is considered obvious to the person skilled in the art to apply this knowledge to the dosage form known from the prior art of D1.

Regarding the second aspect mentioned above, there is no information in present claim 1 on how the rapid release of the H2RA is achieved. It is considered obvious to the person

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Supplemental Box

skilled in the art that such an effect would be desirable in the making of a dosage form based on the knowledge of D1, since it is well known that a delay of the effect of PPI:s is inevitable. Furthermore, it is known from D2 that an unprotected layer containing an antacid agent dissolves rapidly in the acidic milieu of the stomach, exposing the coated tablet core. It is considered obvious to the person skilled in the art to use this to achieve the rapid release of the H2RA.

On the basis of the above argumentation, the invention according to present claim 1 is considered to lack an inventive step with regard to D1 in combination with D2. The remaining claims are considered to contain, in addition to the information in claim 1, only matter of routine character that is obvious to the person skilled in the art.

See also D3-D9. D3 and D5 disclose studies of the combined use of PPI:s and H2RA:s, and in D4 (page 7, line 32 - page 8, line 4; page 21, claim 3; page 24, claim 24; page 28, claim 48) mixtures of PPI:s and H2RA:s are proposed as anti-ulcer medicaments.

The documents D6-D9 are only considered to represent the general state of the art and are of no particular relevance.

In summary, the invention according to present claims 1-39 is novel and has industrial applicability, but is considered to lack an inventive step.

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Inte[redacted] application No.
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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 02083132	24.10.2002	17.04.2002	18.04.2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Present claims 1-39 relate to dosage forms, and to methods for the production of these dosage forms, defined by references to desirable properties, namely "acid-susceptible proton pump inhibitor", "H2 receptor antagonist", "pharmacologically effective amounts", "delayed release and/or extended release", "rapidly released", "capable to raise gastric pH to above 4 within two hours after administration and to keep it above 4 for at least 4 hours", "capable to keep gastric pH above 4 for at least 8 hours", "capable to raise gastric pH to above 3 within 2 hours from administration" and "capable to raise gastric pH above 3 for at least 8 hours".

The claims cover all dosage forms having these properties and all methods for the production of dosage forms having these properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such dosage forms and methods.

Independent of the above reasoning, claims 1-39 also lack clarity (Article 6 PCT), since attempts are made to define a product by reference to results to be achieved.